Contrast-Enhanced Ultrasound Algorithms (CEUS-LIRADS/ESCULAP) for the Noninvasive Diagnosis of Hepatocellular Carcinoma – A Prospective Multicenter DEGUM Study

CEUS-Algorithmen für den kontrastverstärkten Ultraschall (CEUS-LIRADS/ESCULAP) in der nichtinvasiven Diagnostik des hepatozellulären Karzinoms – eine prospektive, multizentrische DEGUM-Studie

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ABSTRACT

Background This prospective multicenter study funded by the DEGUM assesses the diagnostic accuracy of standardized contrast-enhanced ultrasound (CEUS) for the noninvasive diagnosis of hepatocellular carcinoma (HCC) in high-risk patients.

Methods Patients at high risk for HCC with a histologically proven focal liver lesion on B-mode ultrasound were recruited prospectively in a multicenter approach. Clinical and imaging data were entered via online entry forms. The diagnostic accuracies for the noninvasive diagnosis of HCC were compared for the conventional interpretation of standardized CEUS at the time of the examination (= CEUS on-site) and the two CEUS algorithms ESCULAP (Erlanger Synopsis for Contrast-enhanced Ultrasound for Liver lesion Assessment in Patients at risk) and CEUS LI-RADS (Contrast-Enhanced UltraSound Liver Imaging Reporting and Data System).

Results 321 patients were recruited in 43 centers; 299 (93.1 %) had liver cirrhosis. The diagnosis according to histology was HCC in 256 cases, and intrahepatic cholangiocarcinoma (iCCA) in 23 cases. In the subgroup of cirrhotic patients (n = 299), the highest sensitivity for the diagnosis of HCC was achieved with the CEUS algorithm ESCULAP (94.2 %) and CEUS on-site (90.9 %). The lowest sensitivity was reached with the CEUS LI-RADS algorithm (64 %; $p < 0.001$). However, the specificity of CEUS LI-RADS (78.9 %) was superior to that of ESCULAP (50.9 %) and CEUS on-site (64.9 %; $p < 0.001$). At the same time, the negative predictive value (NPV) of CEUS LI-RADS was significantly inferior to that of ESCULAP (34.1 % vs. 67.4 %; $p < 0.001$) and CEUS on-site (62.7 %; $p < 0.001$). The positive predictive values of all modalities were high (around 90 %), with the best results seen for CEUS LI-RADS and CEUS on-site.

Conclusion This is the first multicenter, prospective comparison of standardized CEUS and the recently developed CEUS-based algorithms in histologically proven liver lesions in cirrhotic patients. Our results reaffirm the excellent diagnostic accuracy of CEUS for the noninvasive diagnosis of HCC in high-risk patients. However, on-site diagnosis by an experienced examiner achieves an almost equal diagnostic accuracy compared to CEUS-based diagnostic algorithms.

ZUSAMMENFASSUNG

Hintergrund Diese prospektive, multizentrische, DEGUM-geförderte Studie untersucht die diagnostische Genauigkeit standardisierter Algorithmen für die Kontrastmittelsonografie (CEUS-Algorithmen) in der nichtinvasiven Diagnostik des hepatozellulären Karzinoms (HCC) bei Hochrisikopatienten.

Methoden HCC-Hochrisikopatienten mit histologisch gesicherter Leberläsion im B-Bild-Ultraschall wurden prospektiv multizentrisch eingeschlossen. Klinische Daten und Bildgebungsbefunde wurden über Online-Eingabemasken erfasst. Es erfolgte ein direkter Vergleich der diagnostischen Genauigkeiten für die konventionelle CEUS-Befundung zum Untersuchungszeitpunkt (CEUS-on-site) und die CEUS-Algorithmen ESCULAP (Erlanger Synopsis for Contrast-enhanced Ultrasound for Liver lesion Assessment in Patients at risk) und CEUS LI-RADS (Contrast-Enhanced UltraSound Liver Imaging Reporting and Data System).

Ergebnisse 321 Patienten an 43 Zentren wurden eingeschlossen (93,1 % Leberzirrhose). Der histologische Befund ergab 256 HCCs und 23 intrahepatische cholangiozelluläre Karzinome (iCCA). Die höchste Sensitivität bei Zirrhose-Patienten (n = 299) erzielten der CEUS-Algorithmus ESCULAP (94,2 %) und CEUS-on-site (90,9 %), die geringste Sensitivität der CEUS LI-RADS-Algorithmus (64 %; p < 0,001). Die Spezifität war höher für CEUS LI-RADS (78,9 %) versus ESCULAP (50,9 %) und CEUS on-site (64,9 %; p < 0,001). Der negativ prädiktive Wert (NPW) war für CEUS LI-RADS niedriger als für ESCULAP (34,1 % vs. 67,4 %; p < 0,001) und CEUS-on-site (62,7 %; p < 0,001). Der positiv prädiktive Wert (PPW) war für alle Modalitäten hoch (rund 90 %).

Schlussfolgerungen Dies ist die erste prospektive, multizentrische Studie zum Vergleich der standardisierten Kontrastmittelsonografie mit den kürzlich entwickelten CEUS-Algorithmen in histologisch gesicherten Leberläsionen bei Zirrhose-Patienten. Unsere Ergebnisse bestätigen die exzellente diagnostische Genauigkeit der Kontrastmittelsonografie in der nichtinvasiven HCC-Diagnostik bei Hochrisikopatienten. Die On-site-Diagnose eines erfahrenen Untersuchers erzielt dabei eine beinahe ebenso gute diagnostische Genauigkeit wie die CEUS-basierten Diagnosealgorithmen

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant solid tumor entity worldwide with increasing incidence. Noninvasive diagnosis with contrast-enhanced imaging in high-risk patients is possible if the “characteristic enhancement pattern” is present. According to German national HCC guidelines, the three available imaging modalities (contrast-enhanced ultrasound = CEUS, magnetic resonance imaging = MRI, computed tomography = CT) are considered equivalent [1]. However, as to now, the typical enhancement pattern in HCC for CEUS is defined as “arterial phase hyperenhancement followed by rapid contrast washout” [1] or “nodule ≥ 1 cm in a cirrhotic patient with arterial phase hyperenhancement and late-onset (> 60 seconds) washout of mild intensity” [2]. These definitions have to be questioned as recent studies have shown that especially well-differentiated HCCs show very late, mild washout or even no washout at all [3–6]. Still, arterial hyperenhancement alone in CEUS is not considered sufficient for definite diagnosis of HCC in the cirrhotic liver [7]. Thus, the widespread standard of ending the CEUS examination in the late phase after 2–3 minutes might lead to overlooking those HCCs with very late onset of washout. Most recently, CEUS-based diagnostic algorithms have been developed in an attempt to improve standardization in the reporting and documentation of lesions suspicious for HCC in high-risk patients. Initial studies on this issue suggest good diagnostic accuracy of these algorithms but with some problems still to be resolved [8–12]. Finally, the diagnostic value and clinical feasibility of these algorithms have to be proven. To date, it is unclear whether the CEUS algorithms provide any additional benefit compared to the interpretation of standardized CEUS at the time of the examination.

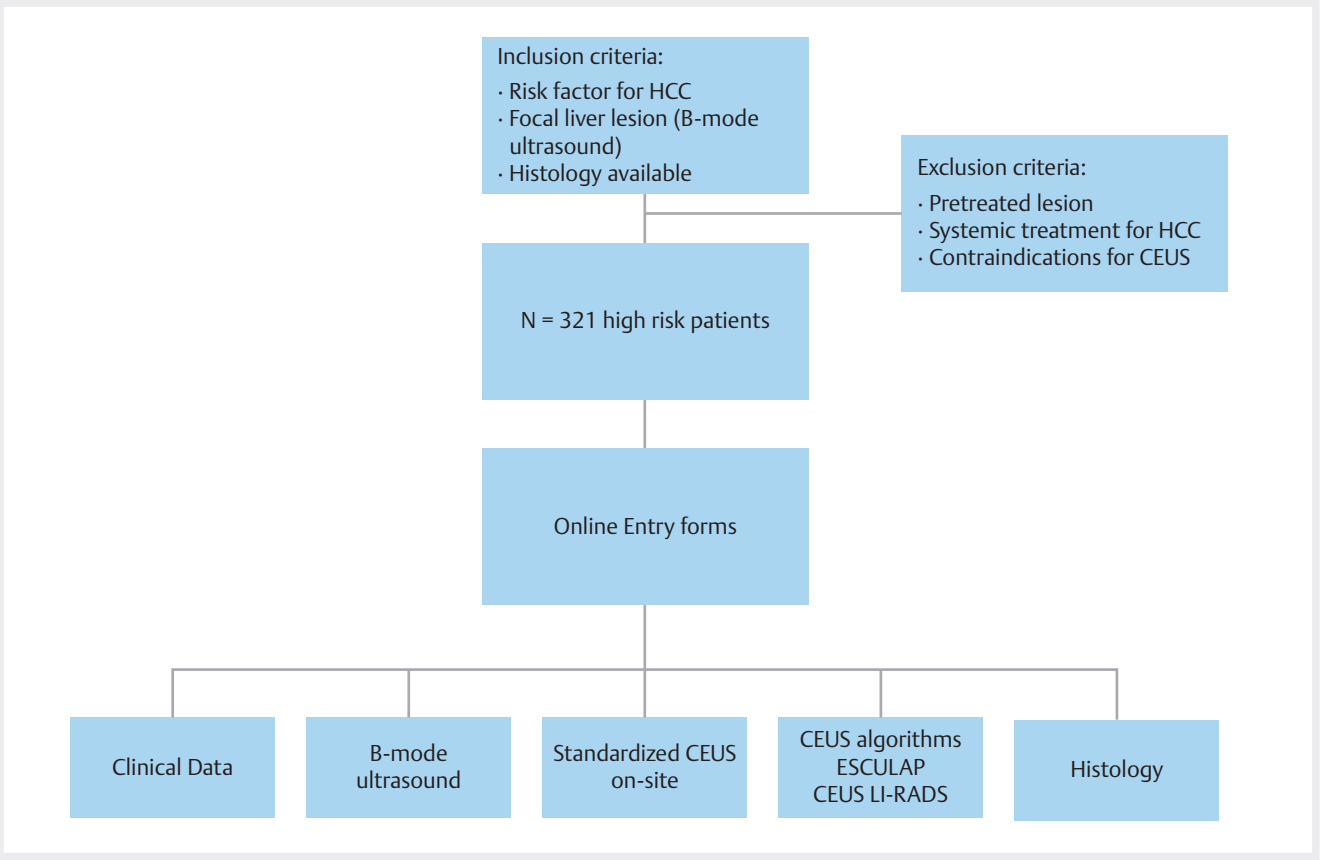
Purpose of the DEGUM CEUS HCC study

The aim of this prospective multicenter study was to assess the diagnostic accuracy of standardized contract-enhanced ultrasound (CEUS) for the noninvasive diagnosis of hepatocellular carcinoma (HCC) in high-risk patients. The study was funded by the German Society for Ultrasound in Medicine (DEGUM). This manuscript contains data on the diagnostic accuracy of the recently developed CEUS algorithms (Erlanger Synopsis for Contrast Enhanced Ultrasound for Liver lesion Assessment in Patients at risk = ESCULAP/Contrast-Enhanced UltraSound Liver Imaging Reporting and Data System = CEUS LI-RADS) in direct comparison to the “conventional” interpretation of standardized CEUS at the time of the examination.

Materials and Methods

Study design

The study design is depicted in ▶ **Fig. 1**. All patients with known risk for HCC based on the national guideline and presence of a focal liver lesion were enrolled into the study. All patients underwent B-mode ultrasound and CEUS. Histological findings were collected from biopsy or surgery. The examiner entered data regarding clinical background, B-mode ultrasound, CEUS on-site (at the time of the examination), and reference standard (histology) into online entry forms via a personalized, password-protected account. All lesions had to be categorized according to the two CEUS algorithms ESCULAP (Erlanger Synopsis for Contrast-Enhanced Ultrasound for Liver Lesion Assessment in Patients at risk) and CEUS LI-RADS (Contrast-Enhanced UltraSound Liver Imaging Reporting and Data System).



▶ **Fig. 1** illustrates the study design.

Patient recruitment

The inclusion criteria were the presence of a solid liver lesion on conventional B-mode ultrasound in a patient at high risk for hepatocellular carcinoma according to the German national S3/AWMF HCC guidelines [1] (i. e., liver cirrhosis of any origin; chronic hepatitis B infection; chronic hepatitis C infection with advanced fibrotic changes; non-alcoholic steatohepatitis (NASH); history of prior HCC); age ≥ 18 years, and the availability of histology as a reference standard. The exclusion criteria were systemic treatment for HCC (both history of systemic treatment and ongoing treatment for HCC), locally treated lesions, age < 18 years, and contraindications for contrast-enhanced ultrasound (such as known allergy or hemodynamic instability). The local ethics committee approved the study (ethics vote 16_17B). All patients provided their written informed consent according to DSGVO 05/2018 (European General Data Protection Regulation) for prospective evaluation of anonymized data.

Contrast-enhanced ultrasound

Contrast-enhanced ultrasound (CEUS) had to follow a standardized protocol with continuous assessment of the arterial phase until the maximum contrast enhancement was reached in the lesion, followed by intermittent scanning with short sweeps through the lesion at the following time points: 1 minute; 3 minutes; 4–6 minutes in case of no contrast washout after 3 minutes [13]. In the case of insufficient contrast enhancement in the late phase, examiners were instructed to apply a second contrast bolus with subsequent assessment of the late phase only.

CEUS algorithms

With the CEUS algorithms, focal liver lesions are categorized following defined criteria (such as lesion size and contrast enhancement behavior) according to their risk of being an HCC. With ESCULAP, there are seven categories: ESCULAP-1 = definitely benign; ESCULAP-2 = intermediate probability of HCC, uncertain findings; ESCULAP-3 = definite HCC; ECULAP-C = intrahepatic cholangiocarcinoma; ESCULAP-V = HCC with tumor invasion of the hepatic veins or portal vein; ESCULAP-X = non categorizable; and ESULAP-Tr = pretreated lesion, which was excluded in this study [8–11]. One main difference with respect to CEUS LI-RADS is that with ESCULAP, lesions ≥ 10 mm in size with arterial phase hyperenhancement but no washout can be categorized as definite HCC. Also, subtotal infiltration of a liver lobe by the tumor is regarded as an additional feature. ESCULAP was defined from a clinical point of view and is adapted to patients at high risk for HCC according to the German national HCC guidelines (cirrhosis of any origin; chronic hepatitis B infection; chronic hepatitis C infection with advanced fibrosis; non-alcoholic steatohepatitis; history of prior HCC). With CEUS LI-RADS, there are eight categories: CEUS-LR-1 = definitely benign; CEUS-LR-2 = probably benign; CEUS-LR-3 = intermediate probability of malignancy; CEUS-LR-4 = probably HCC; CEUS-LR-5 = definitely

HCC; CEUS-LR-M = probably or definitely malignant, not necessarily HCC; CEUS-LR-TIV = tumor in vein; CEUS-LR-NC = not categorizable. The ESCULAP algorithm is shown in ▶ **Supplemental Fig. 1**. The CEUS LI-RADS algorithm is displayed on https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/CEUS-LI-RADS-v2017.

Online entry forms

The following data was collected via the online entry forms: participating center, ultrasound device used, examiner, date of examination; automatically generated patient number, patient age, gender, risk factor for HCC, presence of liver cirrhosis, known extrahepatic malignancy, diabetes mellitus, general condition (ECOG, Eastern Cooperative Oncology Group performance status); findings from B-mode ultrasound: image quality, conditions of liver parenchyma, presence of portal vein thrombosis, presence of transjugular intrahepatic portosystemic stent shunt (TIPS), number of focal liver lesions, size of target lesion, depth location, echotexture of target lesion, macroinvasion of liver vessels, findings within Milan criteria [14]; CEUS on-site findings: image quality, application of second contrast bolus, enhancement behavior of the index lesion relative to the surrounding parenchyma in the arterial phase/after 1 minute/after 3 minutes/after 4–6 minutes in the case of no washout after 3 minutes, presence of enhancing tumor thrombus, diagnosis at the time of the examination according to CEUS; reference standard: histology: histological findings from index lesion; histological findings from liver parenchyma (optional); categorization of the index lesion according to the CEUS algorithms ESCULAP and CEUS LI-RADS. After discussion with the participating centers, we decided against assessment of alpha fetoprotein (AFP) values as there is no clear recommendation for the diagnostic value of AFP in the national HCC guidelines.

Recruitment of participating centers

The study was initiated as a prospective nation-wide multicenter trial and registered as NIH trial (NCT03405909). It was funded by the DEGUM (Deutsche Gesellschaft für Ultraschall in der Medizin/German Society for Ultrasound in Medicine). Via the central registry of DEGUM members, all centers with expertise in abdominal ultrasound including CEUS according to DEGUM Level II-III (at least 6000–10 000 ultrasound examinations) were invited to participate in the study. Moreover, short information about the trial together with initiator contact information was posted on the DEGUM homepage.

Centers were equipped with individual login data and personal passwords to access their individual accounts with the online data entry forms. Prior to the start of the study, participating centers were invited to two meetings with practical training sessions of the online entry forms and the standardized CEUS examination protocol including CEUS algorithms. Arising questions were continuously being answered via personal contact, email, or telephone. Some centers were provided with study contracts according to their needs.

▶ **Table 1** Patient characteristics (n = 321).

	n	%
risk factor based on patient history		
▪ liver cirrhosis	230	71.7
▪ chronic hepatitis B infection	16	5
▪ chronic hepatitis C infection with advanced fibrosis	15	4.7
▪ non-alcoholic steatohepatitis (NASH)	17	5.3
presentation for HCC surveillance	129	40.2
history of extrahepatic malignancy	54	16.8
diabetes mellitus	131	40.8
general condition (ECOG)		
▪ ECOG 0	199	62
▪ ECOG 1–2	117	36.4
▪ ECOG 3–4	5	1.6

HCC: hepatocellular carcinoma; ECOG: Eastern Cooperative Oncology Group performance status.

Statistical analysis

Data was exported from the online entry forms using Microsoft Excel. Quantitative variables are expressed as a mean and range. Categorical variables are expressed as frequencies. Sensitivities, specificities, positive and negative predictive values are shown with 95 % confidence intervals. Imaging modalities were compared separately within the diseased and non-diseased group by McNemar's test. The p-values for the comparison of modalities with respect to predictive values were estimated by the R-package DTComPair using the function pv.gs(), which uses the approach by Leisenring et al. [15]. All p-values below 0.05 were considered statistically significant. Analyses were performed in R 3.5.2 [16].

Results

Participating centers and patient characteristics

43 centers (16 academic centers), referred to as the DEGUM CEUS HCC study group, prospectively recruited a total of 321 high-risk patients with available histological findings. Patient characteristics are shown in ▶ **Table 1**. The mean age was 67 ± 10 years; the predominant sex was male (84.7 %). 299/321 patients (93.1 %) had liver cirrhosis according to patient history, clinical or imaging findings, or histology. Most patients had compensated liver cirrhosis.

B-mode ultrasound

▶ **Table 2** summarizes the B-mode ultrasound findings. Image quality was estimated to be sufficient in 301/321 patients (93.8 %). Most patients had either signs of cirrhosis/steatosis or uncharacteristic parenchymal changes. Only 20 patients (6.2 %) had a normal liver parenchyma.

▶ **Table 2** Findings from B-mode ultrasound (n = 321).

liver parenchyma	
▪ normal parenchyma	20 (6.2 %)
▪ uncharacteristic parenchymal changes not typical of steatosis/cirrhosis	35 (10.9 %)
▪ steatosis	37 (11.5 %)
▪ cirrhosis	229 (71.3 %)
number of lesions	
▪ solitary lesion	197 (61.4 %)
▪ 2–3 lesions	64 (19.9 %)
▪ > 3 lesions	35 (10.9 %)
▪ diffuse tumor infiltration	25 (7.8 %)
size of index lesion (n = 321) [mean ± SD]	5.9 ± 13.3 cm
▪ ≤ 2 cm	48 (15 %)
▪ 2–5 cm	162 (50.5 %)
▪ ≥ 5 cm	111 (34.6 %)
echo texture of index lesion (n = 321)	
▪ hypoechoic	194 (60.4 %)
▪ isoechoic	69 (21.5 %)
▪ hyperechoic	58 (18.1 %)
presence of hypoechoic rim	84 (26.2 %)
macroinvasion of liver veins/portal vein (B-mode, color mode)	34 (10.6 %)
portal vein thrombosis	29 (9 %)
TIPS	9 (2.8 %)
B-mode findings within Milan criteria	147 (45.8 %)

HCC: hepatocellular carcinoma; TIPS: transjugular intrahepatic porto-systemic stent.

Conventional contrast-enhanced ultrasound (CEUS)

CEUS image quality was judged to be sufficient in 277/321 cases (86.3 %). In 74 cases (23.1 %), a second contrast bolus was applied. The diagnosis according to on-site interpretation of standardized CEUS at the time of the examination was HCC in 254 cases (79.1 %). Of the 256 HCCs in the study, 232 were correctly identified (90.6 %). Of the remaining 24 HCCs, 20 were diagnosed as "suspected malignancy", and only 4 (1.6 %) as probably benign lesions. 47 cases (14.6 %) were diagnosed as malignant, but not typical of HCC. In 12 cases (3.7 %), the examiner suspected an intrahepatic cholangiocellular carcinoma (iCCA); in 35 cases (10.9 %), another malignancy was suspected. 20 cases (6.2 %) were assumed to be benign (dysplastic/regenerate node, n = 12; hemangioma, n = 1; focal nodular hyperplasia, n = 3; other, n = 4). "Other" was specified as "cholangioma", n = 1; "peliosis hepatis", n = 1; "perfusion alteration in a patient with portal vein thrombosis", n = 1; and "lesion with unknown benign or malignant nature", n = 1. The special case of HCC with macroinvasion of the liver veins or portal vessels was seen in 34 cases (10.6 %); 15 of these showed contrast enhancement of the tumor thrombus upon CEUS.

▶ **Table 3** Reference standard of the index lesion according to histology (n = 321).

malignant n = 293 (91.3 %)	
hepatocellular carcinoma (HCC) n = 256 (79.8 %)	
▪ G1	64 (25 %)
▪ G2	139 (54.3 %)
▪ G3	44 (17.2 %)
▪ no grading available	9 (3.5 %)
other malignancy n = 37 (11.5 %)	
▪ intrahepatic cholangiocellular carcinoma (iCCA)	23 (7.2 %)
▪ mixed tumor HCC/iCCA	1 (0.3 %)
▪ metastases	12 (3.7 %)
▪ others*	1 (0.3 %)
benign n = 28 (8.7 %)	
▪ regenerate/dysplastic nodule	16 (5 %)
▪ focal nodular hyperplasia (FNH)	2 (0.6 %)
▪ hemangioma	1 (0.3 %)
▪ inflammatory adenoma	2 (0.6 %)
▪ others**	7 (2.2 %)

* Others: angiosarcoma, n = 1.
** Others: "inflammatory pseudo-tumor in patient with Erdheim-Chester's syndrome", n = 1; "necrosis in vasculitis", n = 1; "focal fat/fibrosis", n = 1; inconclusive histology (re-biopsy recommended), n = 4.

CEUS algorithms

Diagnosis according to ESCULAP was HCC (ESCULAP-3, ESCULAP-V) in 274 cases, and iCCA (ESCULAP-C) in 15 cases. With CEUS LI-RADS, HCC (CEUS-LR-5, CEUS-LR-TIV) was diagnosed in 178 cases, and other malignancies including iCCA (CEUS-LR-M) in 44 cases.

165 of the 256 HCCs (64.5 %) were correctly identified with both algorithms. In 88 HCCs (34.4 %), correct diagnosis was made with ESCULAP only; in 1 HCC (0.4 %), only CEUS LI-RADS was correct. Misdiagnosis with both algorithms was seen in 14 HCCs (5.5 %).

Reference standard

Histology

The reference standard of the 321 index lesions according to histological findings is summarized in ▶ **Table 3**. Additional information regarding liver parenchyma histology was available in 79.4 % of cases (255/321), including 237 patients (73.8 %) with cirrhosis or significant fibrosis. Only 18 cases (5.6 %) were without fibrotic or cirrhotic parenchymal changes. Steatohepatitis was found in 13.1 % of cases.

▶ **Table 4** Diagnostic accuracies of the different modalities (CEUS on-site, the diagnostic pattern of HCC according to the guidelines (arterial phase hyperenhancement followed by hypoenhancement), and the CEUS algorithms ESCULAP and CEUS LI-RADS) in direct comparison, compared to the reference standard histology.

modality	sensitivity [%]	specificity [%]	PPV* [%]	NPV* [%]
CEUS on-site	90.9 [87.3 %; 94.5 %]	64.9 [52.5; 77.3]	91.7 [88.2; 95.2]	62.7 % [50.4 %; 75.1 %]
CEUS guidelines (hyper-hypo)	68.6 [62.7 %; 74.4 %]	57.9 [45.1; 70.7]	87.4 [82.6; 92.1]	30.3 % [21.6 %; 38.9 %]
ESCULAP	94.2 [91.3 %; 97.2 %]	50.9 [37.9; 63.9]	89.1 [85.2; 92.9]	67.4 % [53.4 %; 81.4 %]
CEUS LI-RADS	64 [58; 70.1]	78.9 % [68.4 %; 89.5 %]	93.1 [89.1; 97]	34.1 % [26 %; 42.2 %]

N (HCC) = 242; n (non-HCC) = 57. Relating to a prevalence of 80.9 %. 95 % confidence intervals are given in brackets. PPV: positive predictive value; NPV: negative predictive value; HCC: hepatocellular carcinoma.

Diagnostic accuracy of different modalities compared to histology

Data on the diagnostic accuracy of the different imaging modalities is summarized in ▶ **Table 4** for the subgroup of 299 cirrhotic patients. We restricted this analysis to cirrhotic patients as cirrhosis is the one risk factor recognized by all HCC guidelines. However, there were no significant differences between the subgroups of cirrhotic patients (n = 299) and non-cirrhotic patients (n = 22). The cirrhotic group (n = 299) comprises all cirrhotic patients in our patient collective, with diagnosis of cirrhosis based either on medical history (n = 230), clinical findings and imaging (n = 229) or histology (n = 237). There are overlaps between the subgroups. The sensitivity for the diagnosis of HCC in high-risk patients was best when using the CEUS algorithm ESCULAP and the on-site diagnosis at the time of the examination. A significantly lower sensitivity was reached when examiners used the CEUS LI-RADS algorithm ($p < 0.001$). However, the specificity of CEUS LI-RADS was superior to that of ESCULAP and CEUS on-site (both $p < 0.001$). At the same time, CEUS LI-RADS showed a negative predictive value which was significantly inferior to ESCULAP ($p < 0.001$) and CEUS on-site ($p < 0.001$). The positive predictive values of all modalities, which refer to a prevalence of 81 % in our patient collective, were around 90 % for all modalities with the best results for CEUS LI-RADS and CEUS on-site ($p < 0.05$).

Discussion

The main risk factor for the development of HCC is liver cirrhosis. Accordingly, 93.1 % of the patients in our study had liver cirrhosis. Only a minority of patients had findings of unaltered liver parenchyma on B-mode ultrasound (6.2 %) or histology (5.6 %). This finding corresponds to data from the DEGUM multicenter study from 2011, where 216/281 HCCs (76.9 %) occurred in the cirrhotic liver [17]. The pre-test risk for HCC in a cirrhotic liver is high. In our study, 91.3 % of the liver lesions were malignant (293/321); 79.8 % were HCCs, and 7.2 % were iCCAs. These findings are in accordance with the literature reporting a pre-test risk of malignancy of > 80 % for solid lesions in the cirrhotic liver, and a risk ratio of HCC versus metastasis of 18:1 [17–19]. In our patient collective, the ratio of HCC versus metastasis was 21:1. At first glance, this might seem surprising as 16.8 % of patients had a history of unrelated malignancy. However, these finding emphasize the high a-priori risk for HCC in the cirrhotic liver, once again strengthening the importance of HCC surveillance in these patients.

For the noninvasive diagnosis of HCC in cirrhotic patients, the diagnostic accuracy of CEUS on-site was high. Reasons for the excellent performance of CEUS on-site could be the combination of clinical experience and ultrasound expertise, diagnosing an HCC in a tumor with diffuse infiltration of the liver, although the characteristic “hyper-hypo” pattern may be absent. This expertise also seems to top the diagnosis based on the criteria in the HCC guidelines (“hyper-hypo pattern”). All examiners invited to participate in our study were highly experienced in abdominal ultrasound and CEUS (> 6000–10 000 ultrasound examinations), which partly explains the excellent diagnostic accuracy of CEUS on-site.

Direct comparison of CEUS on-site versus the CEUS algorithms showed that the positive predictive value was excellent for all modalities. However, the sensitivities of the CEUS algorithm ESCULAP and conventional CEUS on-site were higher compared to the CEUS LI-RADS algorithm ($p < 0.001$ for both comparisons). About one third of definite HCCs (36 %) were “missed” when using CEUS LI-RADS, with the classification of LR-5 as definitive HCC. This is in accordance with a recent retrospective study in five Italian centers by Terzi et al., which found a sensitivity of 62 % for CEUS LI-RADS (LR-5) for the definite diagnosis of HCC [12]. Thus, about 38 % of HCCs were under-classified with the algorithm CEUS LI-RADS. In another retrospective analysis of 56 histologically proven focal liver lesions ≤ 2 cm in high-risk patients (44/56 HCCs = 78.6 %), Ling et al. found a sensitivity of 72.7 % (32/44) for CEUS LI-RADS LR-5 with a PPV of 86.5 % (32/37) [20]. These findings of lower sensitivity of the CEUS LI-RADS algorithm are reproduced in the prospective real-life setting of our study. However, the strength of CEUS LI-RADS is its high specificity, minimizing

the risk of false-positive results. Therefore, the risk of "over-treating" patients at risk for HCC is low. Yet, this high specificity CEUS LI-RADS is accompanied by a poor sensitivity and negative predictive value.

All in all, a high number of patients will be underdiagnosed, possibly resulting in delayed treatment, compared to a low number of patients with overtreatment. In about 120 patients in our collective, the correct diagnosis of definite HCC would not have been made when using CEUS LI-RADS. From a clinical point of view, the false-positive results are most likely to be dysplastic nodules in a cirrhotic liver. If a dysplastic nodule is treated like an HCC, the harm done to the patient can be expected to be less than if an HCC is overlooked.

In CEUS LI-RADS, the definition of "washout" is defined as washout with late onset (> 60 seconds) and mild intensity. This definition has already entered into the recent European HCC guidelines [2]. Given the poor performance of the "hyper-hypo" pattern without further refinement (as is the case with the last version of, for example, the German HCC guidelines), the "typical" pattern of HCC needs further specification. One purpose of the CEUS algorithms was to overcome this problem by defining the "typical HCC pattern" upon CEUS via several distinct criteria. However, all in all, the advantages of the CEUS algorithms seem limited. Although this was not the subject of our study, it is possible that the CEUS algorithms might be more helpful for less experienced examiners.

A strength of our study is the prospective, multicenter design in a real-life setting and the inclusion of only histologically proven lesions. Of course, this introduces a certain bias since the noninvasive diagnosis of HCC in high-risk patients is currently often possible by means of contrast-enhanced imaging. Thus, it might be argued that our collective contains particularly "difficult" lesions with unclear imaging findings, requiring biopsy. However, for the assessment of diagnostic accuracies, histology remains the gold standard, which is why we chose this approach. Also, it can be assumed that diagnostic accuracies of imaging modalities might even be better, but probably no worse than shown in our results when applied to a collective of "straight-forward" cases, in which histological sampling is not required.

Conclusion

The DEGUM CEUS HCC study provides the first multicenter, prospective comparison of standardized CEUS modalities including the new CEUS-based diagnostic algorithms in histologically proven liver lesions in cirrhotic patients in a real-life setting. Our results reaffirm the excellent diagnostic accuracy of CEUS for the noninvasive diagnosis of HCC in high-risk patients. However, on-site diagnosis by an experienced examiner achieves an almost equal diagnostic accuracy compared to the CEUS-based diagnostic algorithms.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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